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# United States Patent [19]

Audonnet et al.

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[54] **CANINE HERPESVIRUS BASED RECOMBINANT LIVE VACCINE, IN PARTICULAR AGAINST CANINE DISTEMPER, RABIES OR THE PARAINFLUENZA 2 VIRUS**

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**Related U.S. Application Data**

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[52] **U.S. Cl.** ..... **424/199.1**; 424/229.1; 424/704.1; 424/213.1; 435/320.1; 536/23.72

[58] **Field of Search** ..... 424/229.1, 199.1, 424/204.1, 818, 213.1; 935/65; 536/23.72; 435/320.1

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[57] **ABSTRACT**

Disclosed and claimed is a recombinant canine herepes virus (CHV). The recombinant CHV includes and expresses at least one heterologous nucleotide sequence encoding an antigen. The antigen can be canine distemper virus HA, canine distemper virus F, rabies virus G, canine parvovirus VP2, parainfluenza virus type 2 HA, parainfluenza virus type 2 F, *Borrelia burgdorferi* OspA, or *Borrelia burgdorferi* OspB. The at least one heterologous nucleotide sequence can be in at least one insertion site selected from the group consisting of ORF3 (SEQ ID NO:4), ORF5 (SEQ ID NO:5), the thymidine kinase gene, and the intergenic region corresponding to genes coding for the large subunit and the small subunit. Immunological or vaccine compositions as well as methods for inducing an immunological response are also disclosed and claimed.

**31 Claims, 18 Drawing Sheets**

-continued

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What is claimed is:

1. A recombinant canine herpes virus (CHV) comprising and expressing at least one heterologous nucleotide sequence in at least one insertion site comprising ORF3 (SEQ ID NO:5).

2. The recombinant CHV according to claim 1 wherein the at least one heterologous nucleotide sequence encodes an antigen selected from the group consisting of canine distemper virus HA, canine distemper virus F, rabies virus G, canine parvovirus VP2, parainfluenza virus type 2 HA, parainfluenza virus type 2 F, *Borrelia burgdorferi* OspA, and *Borrelia burgdorferi* OspB.

3. The recombinant CHV of claim 1 wherein the at least one heterologous nucleotide sequence is inserted by simple insertion, or after total or partial deletion of the insertion locus.

4. The recombinant CHV according to claim 1 further comprising a strong eukaryotic promoter; wherein at least

one heterologous nucleotide sequence is operably linked to the strong eukaryotic promoter.

**5**. The recombinant CHV according to claim **4** wherein the strong eukaryotic promoter comprises a CMV immediate-early promoter.

**6**. The recombinant CHV of claim **5** wherein the CMV immediate-early promoter comprises a murine or human CMV immediate-early promoter.

**7**. The recombinant CHV according to claim **1** comprising at least two heterologous nucleotide sequences inserted into at least one insertion site wherein each heterologous nucleotide sequence is under the control of a different eukaryotic promoter.

**8**. The recombinant CHV according to claim **7** wherein the eukaryotic promoters are CMV immediate-early promoters of different animal origin.

**9**. The recombinant CHV according to claim **7** comprising a first heterologous nucleotide sequence operably linked to a first promoter and a second heterologous nucleotide sequence operably linked to a second promoter; wherein, the first promoter comprises a CMV immediate-early promoter, and, the first and second promoters are arranged so that their 5' ends are adjacent.

**10**. The recombinant CHV according to claim **2** further comprising at least one heterologous nucleotide sequence encoding an immunomodulatory polypeptide.

**11**. The recombinant CHV according to claim **9** wherein the heterologous nucleotide sequence comprises a nucleotide sequence selected from the group consisting of nucleotide sequences encoding cytokines.

**12**. The recombinant CHV according to claim **1** wherein the heterologous nucleotide sequence comprises an expression cassette comprising from **5'** to **3'**, a promoter, two or more coding regions separated in pairs by an internal ribosome entry site (IRES), and a polyadenylation signal.

**13**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the canine distemper virus HA antigen.

**14**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the canine distemper virus F antigen.

**15**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the rabies virus G antigen.

**16**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the canine parvovirus VP2 antigen.

**17**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the parainfluenza virus type 2 HA antigen.

**18**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the parainfluenza virus type 2 F antigen.

**19**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the *Borrelia burgdorferi* OspA antigen.

**20**. The recombinant CHV of claim **2** comprising and expressing at least one heterologous nucleotide sequence encoding the *Borrelia burgdorferi* OspB antigen.

**21**. The recombinant CHV according to claim **1** wherein the at least one heterologous nucleotide sequence encodes an antigen.

**22**. The recombinant CHV according to claim **1** wherein the at least one heterologous nucleotide sequence encodes an immunomodulatory polypeptide.

**23**. An immunological composition comprising a recombinant CHV as claimed in any one of claims **1** to **20**, or **21** or **22**.

**24**. A multivalent immunological composition comprising, as a mixture or to be admixed, at least a first recombinant CHV and a second recombinant CHV; wherein the first and second recombinant CHV are as claimed in any one of claims **1** to **20** or **21** or **22**, and the heterologous nucleotide sequence in the first recombinant CHV is different than the heterologous nucleotide sequence in the second recombinant CHV.

**25**. A method for inducing an immunological response in a canine comprising administering to the canine a recombinant CHV as claimed in any one of claims **1** to **20**, or **21** or **22**.

**26**. A method for inducing an immunological response in a canine animal comprising administering to the canine an immunological composition as claimed in claim **23**.

**27**. A method for inducing an immunological response in a canine comprising administering to the canine an immunological composition as claimed in claim **24**.

**28**. The method of claim **25** wherein the administering comprises mucosally administering a dose comprising between $10^2$ and $10^5$ CCID50 of the recombinant CHV.

**29**. The method of claim **26** wherein the administering comprises mucosally administering a dose comprising between $10^2$ and $10^5$ CCID50 of the recombinant CHV.

**30**. The method of claim **27** wherein the administering comprises mucosally administering a dose comprising between $10^2$ and $10^5$ CCID50 of the recombinant CHV.

**31**. A method for expressing a polypeptide comprising contacting a suitable cell with a recombinant CHV as claimed in any one of claims **1** to **20** or **21** or **22**.

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